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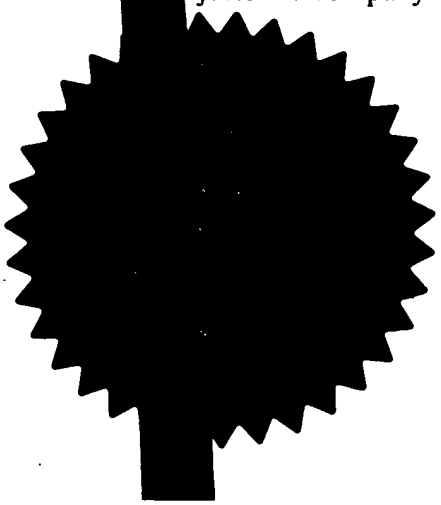

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2. Patent application number *(The Patent Office will fill in this part)* — **9925414.6**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — OPTISCAN LIMITED,
OLD HORSE YARD,
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TOFT,
CAMBRIDGE, CB3 7RY.

   Patents ADP number *(if you know it)* — 7659832001

   If the applicant is a corporate body, give the country/state of its incorporation — UNITED KINGDOM

4. Title of the invention — IMPROVEMENTS IN OR RELATING TO THE INVESTIGATION OF SKIN HISTOLOGY

5. Name of your agent *(if you have one)* — ~~Barker Brettell~~

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* — ~~138 Hagley Road~~
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   ~~Birmingham~~
   ~~B16 9PW~~

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Country	Priority application number *(if you know it)*	Date of Filing *(day/month/year)*

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Signature [signature] Date 27 October 1999

Barker Brettell

12. Name and daytime telephone number of person to contact in the United Kingdom: Mr. A.H. Tebbit Tel: 0121 456 1364

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IMPROVEMENTS IN OR RELATING TO THE INVESTIGATION OF SKIN HISTOLOGY

This invention relates to the investigation of skin histology.

In order to understand the purpose of this invention, it is first necessary to have an appreciation of the structure of normal skin.

The skin is divided into two main layers, the epidermis and the dermis, each of which is itself divided into several sub-layers. Starting from the deepest layer, the subcutaneous layer is overlain by a reticular layer of the dermis which is composed of coarse and dense interlacing bundles of collagen fibres ("type 1 collagen") which are intermingled with reticular fibres and elastic fibres. Over this is the papillary dermal layer which is also composed of collagen fibres but these are much finer than those of the reticular layer in that they are not bundled together. The collagen in the papillary dermis is called "type 3 collagen", and it constitutes connective tissue joining the epidermis and the reticular layer of the dermis. The dermis is also rich in blood vessels. The papillary dermis is located immediately beneath the epidermis and is separated from it by the basal lamina. The dermo-epidermal junction is highly irregular in profile due to dermal papillae projecting up from the dermis between rete ridges or pegs projecting down from the epidermis. It is the presence of these rete ridges or pegs and papillae which gives the skin elasticity, and their interaction also provides an anchor for the epidermis. Epithelium cells multiply continuously in a germinative layer, just above the basal lamina, to replace cells lost from the surface of the epidermis. The germinative layer, which is fed by blood vessels leading through the dermis, also contains melanocytes for the production of melanin. The epithelium cells from the germinative layer move upwards into the layer above, the spinous layer, and thence into the granular layer where the cells contain

granules which are involved in the formation of keratin. It is in this granular layer that the cells of the epidermis die. Above the granular layer, is a clear and translucent layer and above that is the outermost layer, the cornified layer. This is composed of clear dead scale-like skin which is progressively lost from the surface by exfoliation.

Historically, dermatological investigations have taken place by biopsy, that is by surgical removal of samples of skin tissue followed by microscopic examination of thin sections of the skin tissue usually viewed at right angles to the skin surface. The information obtained is limited in area to the thin section, unless a number of sections is examined. Each section requires to be cut, stained and mounted onto a microscope slide, and they are therefore time consuming to prepare. Further the technique is invasive, and there may be a consequent risk of infection either at the biopsy site or from the biopsied material, or both, unless stringent precautions are taken.

We have recently proposed non-invasive techniques for investigating skin histology, see for example European Patent Application No 97 9 12 388.2 (WO 98/22023) and British Patent Application No 99 12 908.2, and the present invention is based on further research developing those proposals.

In normal circumstances, the healthy epidermis is translucent and transmits light diffusely; a proportion of incident light will be absorbed in the epidermis, depending in part on the amount of melanin present in the epidermis, and a proportion will be transmitted through to the dermis. Because the papillary dermis largely consists of type 3 collagen, that is, a very fine network of collagen fibres (as low as 2μm in diameter), light passing through the papillary dermis will be subject to Rayleigh scattering. A proportion of the incident light will be scattered inwards

and a proportion will be back-scattered, and some of this scattered light will be remitted back through the epidermis. In the reticular dermis the fibres are of type 1 collagen, that is, they are clumped or bundled together, and they are largely parallel to the skin surface: thus they are too coarse to give rise to Rayleigh scattering, and light penetrating to the reticular dermis will continue until absorbed or deflected by some discontinuity.

Thus light remitted by the epidermis will have its spectral characteristics altered by the effects of melanin, blood and other chromophores in the skin.

The mean thickness of the papillary dermis can vary quite considerably as between one part of the body and another, for example, and in particular, the height and population density of dermal papillae tends to increase according to the stress to which a particular area of skin is habitually subjected. Thus, the thickness of the papillary dermis over a joint will tend to be greater than that over a relatively non-stressed region such as the lower back. These variations, and variations between different subjects will have a marked effect on the skin colour, but as we have previously noted (see WO 98/22023), it is possible to construct a mathematical model which allows corrections to be made for this effect. When so corrected it is notable that the colour of normal healthy human skin lies in a well defined surface area within a particular colour space, for example the CIE LMS colour space. That surface area encompasses all colours of normal healthy human skin irrespective of the amount of melanin within the skin and thus irrespective of race or degree of tanning. This approach allows parameters relating to chromophores within the skin to be measured in a more accurate and repeatable way through optical means than was permitted by previously existing techniques.

Our copending British Patent Application No 99 12 908.2 is particularly directed to investigating the concentrations of a number of specific chromophores at different depths within the different layers of the skin.

Our previous proposals have concentrated on identifying and measuring the presence, depth and concentration of chromophores within the skin. The presence and extent of chromophores within the skin is considered to be an important indicator of a variety of ailments and other conditions, and is potentially useful for the preliminary screening of patients to identify those who should be referred to an appropriate clinician for diagnosis and further to assist the clinician in diagnosis and in some cases to indicate whether a given treatment would be of value to the patient.

The present invention has as its principal aim to provide a method and apparatus for providing information on the internal structure of skin which may be of value in research or in assisting a clinician to arrive at a diagnosis of a particular condition of the skin, or for other purposes.

The present invention relates to apparatus for and methods of monitoring light remitted from human skin or images thereof in order to map the papillary surface of the dermis.

According to the present invention, there is provided a method of mapping the papillary surface of an area of the dermis which comprises illuminating the surface of the skin over that area with light and monitoring the intensity of the light remitted from along at least one line or sequence of points, the light having a wavelength sufficiently far into the infra-red that its absorption by melanin and blood is negligible, or having at least two wavelengths of which at least one is in excess of 600nm and deriving therefrom a theoretical intensity of remitted light which is independent of the presence of melanin or blood, and from the

remitted light intensity deriving a signal corresponding to the concentration of type 3 collagen along the or each line or at each point, and producing a contoured image in which the apparent elevation of any point is dependent upon the strength of such signal.

The invention includes apparatus for mapping the papillary surface of an area of the dermis which comprises a light source illuminating the surface of the skin over that area with light which either has a wavelength sufficiently far into the infra-red that its absorption by melanin and blood is negligible, or which has at least two wavelengths of which at least one is in excess of 600nm, means for monitoring the intensity of the light remitted along at least one line or sequence of points, and deriving therefrom an intensity or theoretical intensity of remitted light which is independent of the presence of melanin or blood, and means for deriving a signal from the remitted light intensity corresponding to the concentration of type 3 collagen along the or each line or at each point, and for producing a contoured image in which the apparent elevation of any point is dependent upon the strength of such signal.

The invention thus provides a way of obtaining a map which indicates the contours of the papillary surface of the dermis. In its simplest form, this map is simply a line such as may be seen on a suitably prepared section of biopsied skin. However, such line may be derived without incision and accompanying risk of infection, and it may also be derived and inspected very much more quickly.

The present invention is based on a realisation that the thickness of the papillary dermis may be obtained by utilising the property of human skin to vary its absorption of red and infrared radiation with varying papillary dermis thickness. In general, there is an inverse relationship between

absorption and thickness. The fact that red or infrared radiation is also absorbed by other materials within the skin, particularly melanin and blood, is a complicating factor. However the effect on absorption of varying blood and melanin content is far smaller than the effect of papillary dermis thickness, and so the layer may still be measured. This can be done by obtaining two red or infrared images, each at a different wavelength. The chosen wavelengths are not important, but one should be further into the infrared (i.e. at longer wavelength) than the other. Suitable wavelength bands are 800-1000nm and 600-800nm, in that readily available infrared films and filters may be used. The brightness of points within the image obtained at the longer wavelength is affected to a greater extent by variations in the papillary dermis thickness. Conversely, the image obtained at shorter wavelength will be affected to a greater extent by other materials such as melanin and blood. (In fact when operating sufficiently far into the infrared, say at 1100nm, the effects of melanin and blood become negligible, and it is possible to derive the necessary information using a single wavelength measurement. But this greatly increases the cost of the detection and monitoring equipment.) By predicting the brightnesses of points of differing papillary dermis thickness and amounts of epidermal melanin which absorb near-infrared radiation at the two different infrared wavelengths, a reference graph (Fig 1) can be obtained which consists of lines of constant papillary dermis thickness, wherein Primary 1 is the measurement made at the longer (800-1000nm) wavelength and Primary 2 is the measurement made at the shorter (600-800nm) wavelength. The absorption of blood within these wavelengths is very small (a hundredth of its peak value for visible wavelengths at 600-800nm and even less for 800-1000nm) and to a first approximation may be ignored. Thus, by comparing values obtained at these wavelengths with this graph, it is possible to ascertain the papillary dermis thickness. However it is within the scope of the present

invention to measure brightness at such a long infra-red wavelength e.g. 1100nm that the brightness would vary to such a negligible extent with melanin and blood content that it would effectively depend solely on the papillary dermis thickness. In such a case only one set of brightness measurements would be required.

To calculate the look-up graph shown in Fig 1 the spectral remittance of light from human skin can be calculated given knowledge of the quantity and position of substances within it. Such calculations can be performed using a variety of mathematical means including monte carlo modelling and the Kubelka-Munk theory generating a value for P_n where

$$P_n(\rho, d_m, \nu) = \frac{\int_0^\infty R(\rho,\nu)\theta(\lambda,d_m)^2 S(\lambda) S_{P_n}(\lambda) d\lambda}{\int_0^\infty S(\lambda) S_{P_n}(\lambda) d\lambda}$$

where P_n represents the calculated or measured ratio of remitted to incident light for a particular wavelength function or filter $S_{Pn}(\lambda)$ and incident light $S(\lambda)$. θ represents the light absorbed within the epidermis with d_m representing the quantity of epidermal melanin. R represents the light remitted from the dermis with ρ representing the quantity of blood and ν the thickness of the papillary dermis. P_n can also be obtained through measurements on real skin rather than by calculation.

This analysis can be extended to a more general case

$$P_n(\rho_1,\rho_2,\rho_3,\ldots,\rho_n,d_1,d_2,d_3,\ldots,d_n,\phi_{m1},\phi_{m2},\phi_{m3},\ldots,\phi_{mn},d_m,\nu,\kappa) =$$

$$\frac{\int_0^\infty R(\rho_1,\rho_2,\rho_3,\ldots,\rho_n,d_1,d_2,d_3,\ldots,d_n,\phi_{m1},\phi_{m2},\phi_{m3},\ldots,\phi_{mn},d_m,\nu)\theta(\lambda,d_m,\kappa)^2 S(\lambda) S_{P_n}(\lambda) d\lambda}{\int_0^\infty S(\lambda) S_{P_n}(\lambda) d\lambda}$$

Where κ represent the amount of keratin and ρ_1, ρ_2, ρ_3, ..., ρ_n, the quantity of blood within n planes within the dermis parallel with the skin surface of thickness d_1, d_2, d_3, ..., d_n. Within these planes, ϕ_{m1}, ϕ_{m2}, ϕ_{m3}, ..., ϕ_{mn}, represent the quantity of melanin within the dermis. As with the simple case P_n can also be obtained through measurements on real skin rather than by calculation. For a detailed discussion of this technique please refer to *"A non-invasive imaging system for assisting in the diagnosis of melanoma" University of Birmingham, Symon Cotton, 1998.*

The above discussion relates to measurements of the thickness of the papillary dermis alone. However, according to [Histology a text and atlas, second edition, Michael Ross and Lynn Romrell, Published by Williams & Wilkins] "The papillary layer consists of loose connective tissue. It is located immediately under the epidermis and is separated from it by the basal lamina. The papillary layer is a relatively thin layer extending into (and, thus, also constituting) the dermal papillae and ridges." In contrast the junction between the papillary dermis and reticular dermis is relatively smooth or at least varying with a wavelength very large in contrast to the undulations of the papillary dermis.

It is apparent from this as the thickness of the papillary dermis, v, refers to a particular sampling point, or rather the average over a sampling area, measurements taken at a variety of points return information on the thickness of the papillary dermis at these points. Further to this if it is assumed that the papillary dermis constitutes the dermal papillae and also that the junction between the papillary dermis and reticular dermis is smooth, or at least varies on a scale much larger than the dermal papillae, measurements made from a series of points *v1, v2, v3, ..., vn*, as shown in Fig. 2, will - if displayed spatially - show the undulations in the

papillary dermis. Further measurements can be performed on the height of a particular dermal papilla by subtracting a local minimum, shown in Fig. 2 as min1 ($v2$), from a local maximum, shown in Fig. 2 as max1 ($v1$). Examples showing dermal papillae generated using this method are shown in Figs 6 and 7.

As discussed further by Ross and Romrell "They [dermal papillae] are complemented by what appear to be a series of similar projections or evaginations, called epidermal ridges or rete ridges, which project into the dermis." [Histology, a text and atlas, second edition, Michael Ross and Lynn Romrell, Published by Williams & Wilkins]. It is clear from this that information regarding the rete ridges can be obtained in a similar manner as the rete ridges and dermal papillae fit together and are therefore the inverse of one another. For instance the depth of an individual peg being calculated from max1 – min1. To generate a 3d representation or 2d segment showing a number of rete ridges requires a calculation, C-vn , where C is a constant greater than any of the max1-max2 measurements.

It is apparent from this that measurements of the papillary dermis thickness, v, measured over an area or along a line when suitably interpreted can impart information regarding the dermal papillae and rete ridges. In particular if the thickness of the papillary dermis is measured over an area or along a line and then shown graphically the undulations of the dermal papillae can be observed. As the rete ridges extend down from the epidermis filling the void between the dermal papillae it also becomes evident that the inverse of such a measure – such as a constant value minus the papillary dermis thickness - gives information regarding the rete ridges.

An example of this is shown in Fig. 9 where the dermal papillae pertaining to an area of skin in the shoulder region are shown rising from the dermis. In conjunction with this the rete ridges can be seen descending.

In the most preferred embodiments of the invention, means is provided for monitoring the intensity of the light remitted from a plurality of lines or a two-dimensional array of points, and preferably with a resolution of at least 20 lines or dots per mm.

This allows the production of an analogue of a three-dimensional image which can be printed or displayed on a monitor screen, and in the latter case, the use of suitable software will enable the image to be rotated so that its appearance can be viewed from a plurality of different angles.

A higher resolution may be obtained, and will indeed be necessary if inspection of a highly magnified image of the remitted light is to be obtained, but our tests have shown that a very high resolution is not necessary for many purposes. In a particularly preferred apparatus, an image of remitted light is captured using a digital camera in which use is made of a charge coupled device measuring 20 × 15 mm with a resolution of 800 × 600 pixels.

Such an image may take the form of a series of lines each of which follows the contour of the mapped surface while remaining constant in one of three orthogonal axes. Alternatively, it may comprise lines of equal contour, or it may be constituted as a continuous tone or coloured picture of the papillary surface over the area being inspected.

It is implicit in what has been stated above that no account is taken of any variations in the shape of the boundary between the papillary dermis and the reticular dermis at the intradermal junction. It is assumed that the intradermal junction is flat. In fact, as mentioned there are variations in the thickness of the papillary dermis when the presence of those papillae is discounted, but those variations are of long wavelength in comparison with variations due to the papillae and they may be neglected.

Inspection and analysis of the architecture of the dermal papillae and the epidermal rete ridges at the dermo-epidermal junction allows information to be derived which is of considerable importance to clinicians in order to assist them in diagnosing or assessing the progress of a range of dermatological phenomena.

Examples include the blistering diseases *Pemphigus vulgaris* and bullous pemphigoid. While these diseases appear clinically similar, they have very different prognoses and they require different management. *Pemphigus vulgaris* manifests itself as blisters within the thickness of the epidermis which do not distend the local dermo-epidermal boundary architecture, and it is potentially fatal with a 10% mortality rate. Bullous pemphigoid, however, gives rise to subepidermal blistering which does distend the local dermo-epidermal boundary architecture: prognosis is good, and the disease tends to subside over a number of months.

The dermo-epidermal boundary architecture is important in the differentiation between benign and malignant melanoma, and in identifying the presence of fibrosis within a melanoma. It is also important when assessing the extent of basal cell carcinomas and squamous cell carcinomas.

A preferred embodiment of the present invention will now be described in greater detail with reference to the accompanying diagrammatic drawings, in which:

Figure 1 is a graph showing variation of brightness with papillary dermis thickness for primaries 1 and 2 as described hereinabove,

Figure 2 shows measurements of the dermal papillae and rete ridges, also as described hereinabove,

Figures 3 to 5 are diagrammatic representations of sections through human skin such as may be revealed by conventional biopsy techniques,

Figures 6 and 7 are representations of the dermo-epidermal boundary such as may be mapped by the present invention

Figure 8 is a schematic diagram of apparatus according to this invention, and.

Figure 9 shows representations of the rete ridges (top) and dermal papillae(bottom) from an area of skin ascertained by using the technique of the present invention.

Figure 10 shows a representation of a basal cell carcinoma ascertained by using the technique of the present invention.

Figures 1 and 2 have been mentioned above.

Figure 3 is an illustration of a section through normal healthy skin showing the epidermis, the papillary dermis and the reticular dermis, and

shows the irregular dermo-epidermal boundary formed between the papillary dermis and the epidermis by the interpenetrating dermal papillae and the rete ridges of the epidermis.

Figure 4 is an illustration of a section through skin showing a blister due to bullous pemphigoid which gives rise to subepidermal blistering which distends the local dermo-epidermal boundary architecture.

Figure 5 is an illustration of a section through skin showing a blister due to *Pemphigus vulgaris* which is located within the thickness of the epidermis and which do not distend the local dermo-epidermal boundary architecture.

Figures 6 and 7 are maps of the dermo-epidermal boundary provided by the adoption of the present invention, each representing a skin area of about 0.75 mm square.

In both cases the skin is normal. The shallow papillae and rete ridges shown in Figure 6 indicate that the skin is from an area which is not subject to high stress in the day-to-day life of the subject. It is in fact from the lower back. In Figure 7, the dermo-epidermal boundary is more sharply corrugated and with a shorter wavelength, indicating a greater stress to that area arising from the day-to-day life of the subject. The Figure 7 map is of skin from the shoulder. The greater degree of corrugation is associated with a greater need for elasticity and/or a greater need for a resistance to shear between the epidermis and the dermis.

Referring now to Figure 8, a light source 1 is arranged to direct a beam of light onto a first filter wheel 2 which contains a number of holes 21 to 26 each of which may selectively be brought into the light path. One such hole is left empty for the direct transmission of light from the light source

1, while the remainder contain screens, for example of stainless steel wire gauze which serve as grey-scale filters, cutting down light-transmission without affecting its spectral characteristics. The number of grey-scale filters may be as high or as low as desired. Behind the first filter wheel 2 is a second filter wheel 3 which accommodates a number of colour filters. Four such filters 31 to 34 are shown. Again, the number of colour filters may be as high or as low as desired. One such filter may be absent for the direct transmission of light.

The colour filters would together cover as much of the spectrum as required, for example from the infra red, through to the ultra violet. For the purpose of reliably measuring the concentration of type 3 collagen, it would be possible to operate at a single wavelength of around 1050 nm, for example using a 10 nm full width-half maximum bandpass filter centred on that wavelength. This is because the absorption of light of that wavelength by melanin is negligible. However, sensors which are capable of operating in that region are expensive and it is preferred to use longer wavelengths and to take measurements at two different wavelengths where the absorption characteristics of melanin and blood are different so that melanin and blood concentrations can be calculated and/or compensated for. It is in particular preferred to use two 10 nm full width half maximum bandpass filters respectively centred on 694 nm and 940 nm. Other colour filters may be used as desired for monitoring particular wavelengths or wavelength bands. A particularly preferred filter set includes five 10 nm full width half maximum bandpass filters respectively centred on 420, 568, 580, 694 and 940 nm, and three broad band (80 nm) filters centred on 450, 550 and 650 nm.

The reason for using grey-scale filters is that a rather high intensity light source is required for obtaining measurements in the infra-red region due

to the low transmission of colour filters passing light of such wavelengths. In fact we presently prefer to use a xenon light source rated at 300 Watt. Direct transmission of such light, or transmission through for example a yellow filter could burn out a sensor suitable for monitoring in the infra-red. The use of a suitably selected set of grey-scale filters enables a single light source and a single sensor to be used, and this simplifies the apparatus and keeps costs down. A suitable set of grey-scale filters comprises those passing 50, 10 and 1 % of incident light

The light is passed to a bundle of optical fibres 4 through which it is transmitted to the skin S of the patient, or even to an appropriate photographic image of that skin, via a polarising filter 41. Remitted light is carried back through a second polarising filter 51 and a second bundle of optical fibres 5 to a photo-receptor unit 6.

The two polarising filters 41, 51 are set so that their respective planes of polarisation are at right angles, to eliminate specularly reflected light.

The photo-receptor unit 6, which may simply measure the intensity of the remitted light where a series of colour filters is used as illustrated, emits a signal to a comparator 7 which may be constituted as a suitably programmed PC.

As previously mentioned, the photo-receptor is suitably a CCD array, for example a 20 × 15 mm array adapted to resolve 800 × 600 pixels.

The use of the bundles of optical fibres adds greatly to the convenience of use of the apparatus since a relatively small unit at the end of a flexible lead may thereby be brought to the patient's skin S: thus the physical posture of the subject during measurement is largely irrelevant and he or she may be made as comfortable as possible.

The comparator 7 is arranged to process the signals received which relate to the intensity of light remitted at the wavelengths 694 nm and 940 nm, and to derive therefrom a signal proportional to the concentration of type 3 collagen.

The comparator 7 is suitably arranged to supply the results for each pixel monitored via a processor 8 to a display monitor 9 and/or to a printer 10. The processor 8 is arranged to take the signal proportional to the collagen concentration and to use that signal as a measure of altitude to generate a relief map for printing or display. The processor 8 is suitably programmed to allow rotation of the display of the relief map. Examples of such relief maps which show the architecture of the dermo-epidermal boundary constitute Figures 4 and 5 of this specification.

The present invention at least in its most preferred embodiments, enables the generation of information regarding a number of features of any skin being examined. To allow an accurate diagnosis of disorders of the skin, or the prognosis of treatment for such disorders, or the monitoring of healthy skin, it is important that the spatial relationship between these features can be understood. Such an understanding of the dermo-epidermal boundary is greatly facilitated by preferred embodiments of the present invention in which such a map is provided. Such a map may be provided within seconds. Previously, examination by biopsy could reveal contours along a single line section, or more than one section if sufficient biopsy material was taken, but it would be at least several hours and could well be several days before the results were available to the clinician.

The comparator 7 may also receive signals relating to the intensity of light remitted in the red, yellow and blue regions of the spectrum, and of remitted white light. The comparator is arranged to assign a notional position in a colour space according to co-ordinates represented by these

red, yellow and blue values and to note that position having regard to the infra-red value. Instead of measurements over the three primary wavebands, other filters may be provided so that the visible spectrum is split up into four or more wavebands. This establishes four or more co-ordinates, and the comparator may thus assign a notional position in a colour space having four or more dimensions. That position can be unique as representing the presence, depth, offset and concentration of any one or more of a range of chromophores within the skin. The comparator is suitably arranged to supply these results to a display monitor 9 and/or to a printer 10, and it may be arranged to pass control signals to the power supply 11 of a medical laser 12 or other source of radiation whether coherent or non-coherent.

The monitor 9 may be and preferably is provided with a touch screen whereby any of the various operational or programming steps may be initated.

In some preferred embodiments of the invention, a mask is provided to surround the area of skin being illuminated and remit light back to the photoreceptor 6. The incorporation of a standard reflector into such a mask simplifies calibration of the apparatus.

Thus by making use of the invention it is possible to obtain images which correspond to: (a) the visual appearance of the skin surface; (b) the architecture of the dermo-epidermal boundary; and (c) the presence of any chromophore within the skin, including its depth and concentration, and an indication of its nature.

To facilitate the spatial correlation of two or more of such images, for example one showing the appearance of the skin and another showing a particular feature, or of two images showing different features, we have

developed a technique whereby a further image is generated. Thus we also provide a method of and apparatus for showing both images together with the proportion or intensity of each adjusted through the use of a control of some means and this allows spatial correlation of the input images. For example the two original images might be supplied in overlapping relation to a monitor screen of a PC, and the two images be relatively faded in and faded out in order to change from viewing one image to another. This allows correlation between the surface appearance of skin and any underlying feature which might have given rise to that appearance. It is of particular interest in the examination of any lesion in the skin.

The display first shows an image, which may or may not be magnified, of the lesion as it actually appears to the eye or a surface microscopy view or an image taken using cross polarised illumination or an image showing a particular feature. By selecting a particular feature such as blood or areas of melanin invasion into the dermis or melanin within the epidermis etc. the display can then be faded to show this feature as an image. The fading allows a progression, or mixing, between the two views and is a convenient means of allowing a spatial correlation to be made between the features and the lesion image.

The images may be images representing the presence of particular existing features of the skin or one or more of them may be computer generated images representing the predicted effects of a treatment such as a laser irradiation treatment. For example, as mentioned above, it is possible to generate a colour representation of the expected result of a laser irradiation treatment, and it would be possible to generate one such image for each of a set of different irradiation intensities. This would enable a comparison of the different courses of treatment and would allow

selection of an appropriate treatment, for example the one giving the most cosmetically acceptable result.

The analysis afforded by the present invention is also of value in the selection of the wavelength or wavelengths of any light (infra-red, visible or ultra-violet) irradiation treatment that may be indicated. For example, a knowledge of the constituents of a lesion allows a selection of a wavelength of light radiation which will be most strongly and preferentially absorbed by constituents of that lesion. Also, a knowledge of the existence and structure and composition of overlying tissue (including any discontinuities which it might contain) allows the most favourable compromise to be reached between low absorption in the overlying tissue and high absorption in the lesion to be destroyed, thus providing the most effective treatment with the lowest radiation dosage. Thus a laser of an appropriate wavelength may be selected, and/or a variable wavelength laser may be tuned, or an appropriate filter set may be used in conjunction with a source of non-coherent radiation.

As illustrated by Fig. 10, the dermo-epidermal boundary architecture is important *inter alia* for assessing the extent of basal cell carcinomas. Figure 10 is a map of the dermo-epidermal boundary which includes a part affected by such a carcinoma. The contrast between well developed and distinct papillae of healthy skin to the left of the Figure and the area of almost destroyed papillae at the upper right section of the Figure is well marked and clearly shows the boundary of such a carcinoma. The information imparted by such a map of the dermo-epidermal boundary is plainly of value in assisting diagnosis and in the planning of surgical excision boundaries.

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Fig. 1

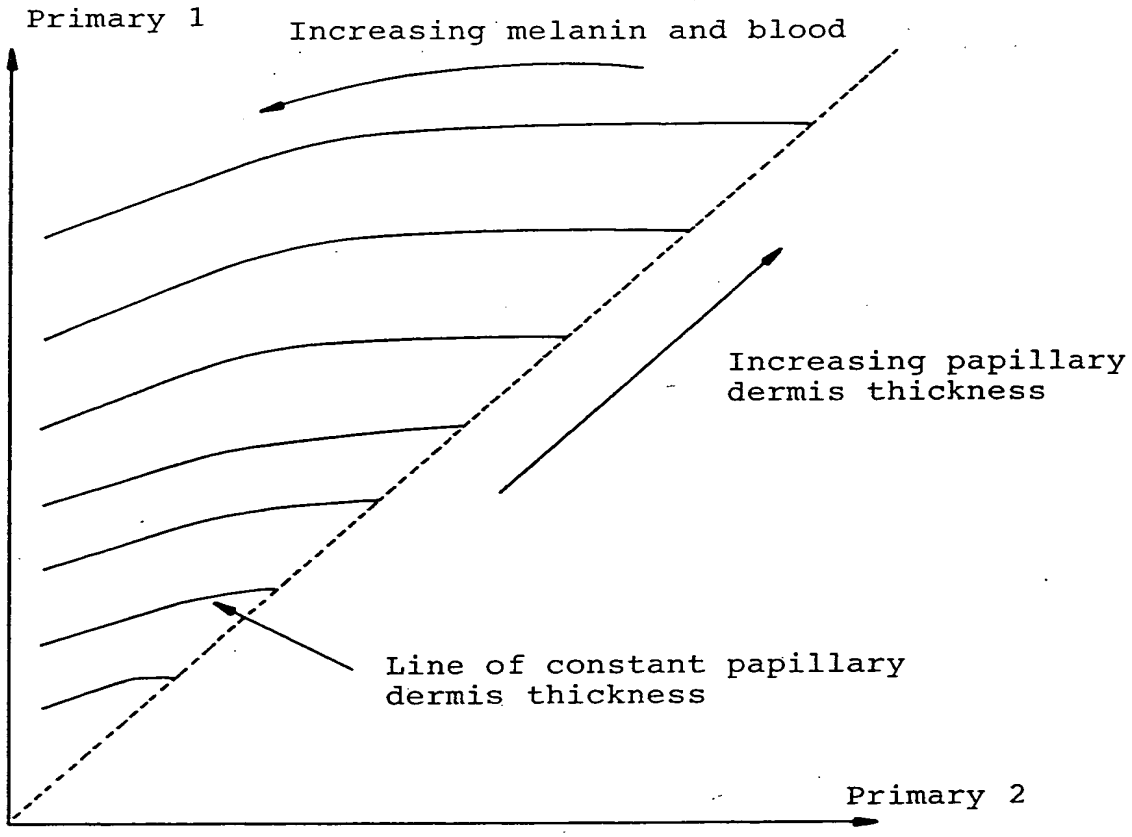
Primary 1
Increasing melanin and blood
Increasing papillary dermis thickness
Line of constant papillary dermis thickness
Primary 2

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Fig. 2

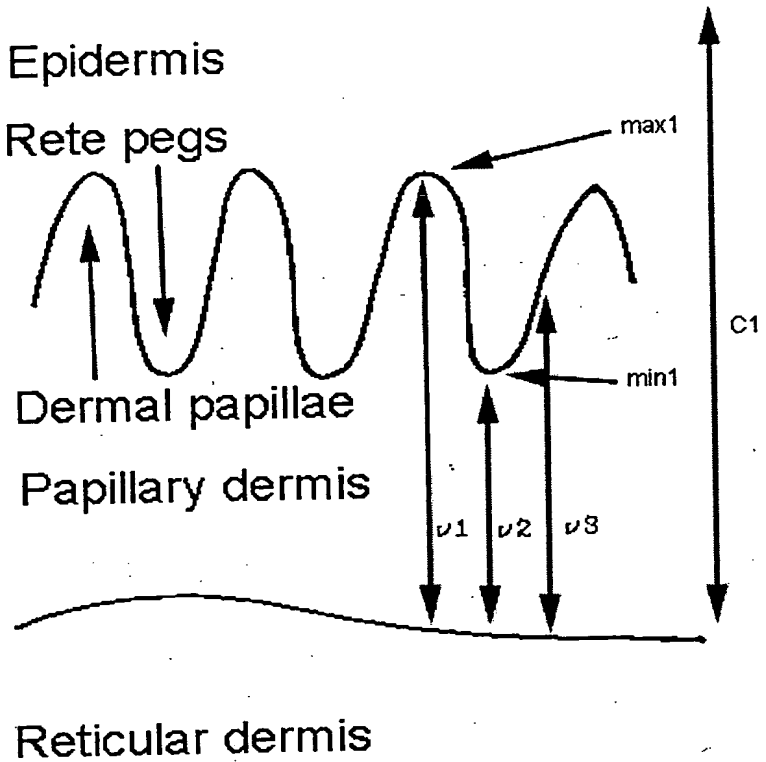
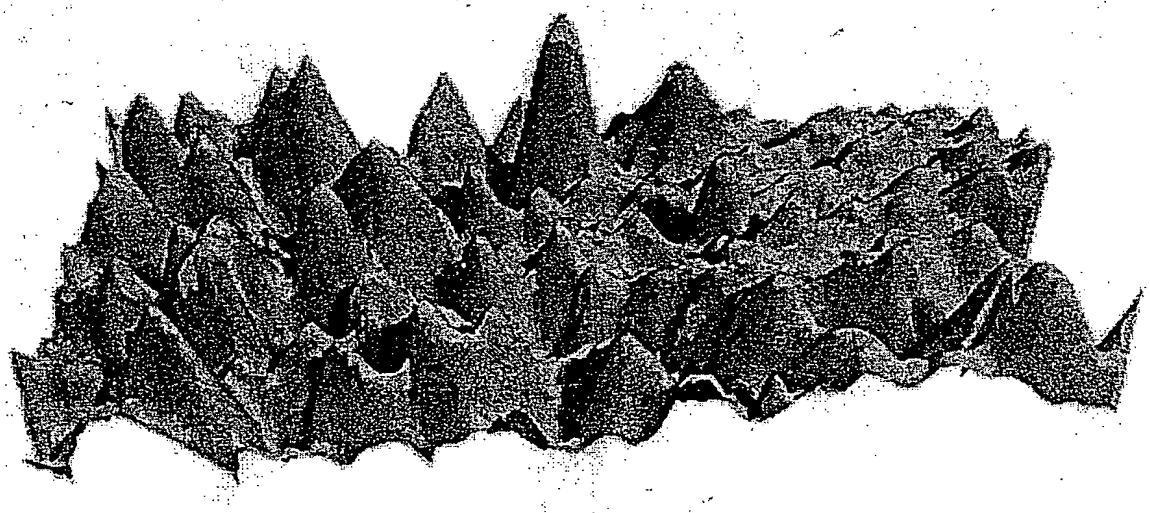


Fig. 10



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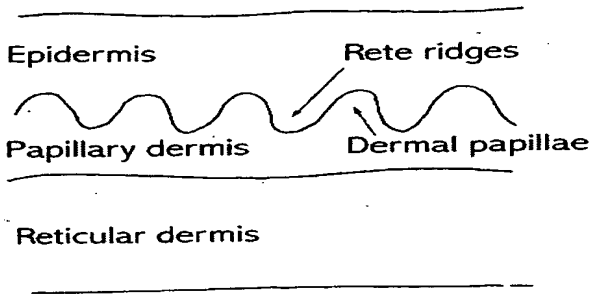

Fig. 3

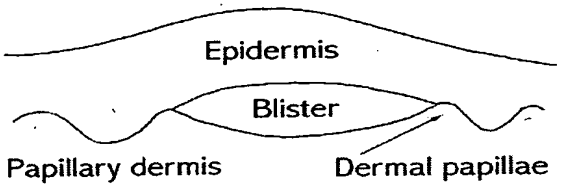

Fig. 4

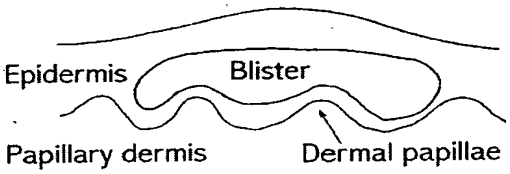

Fig. 5

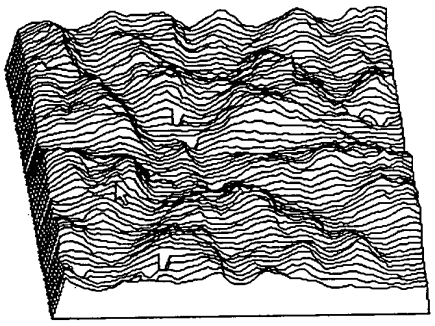

Fig. 6

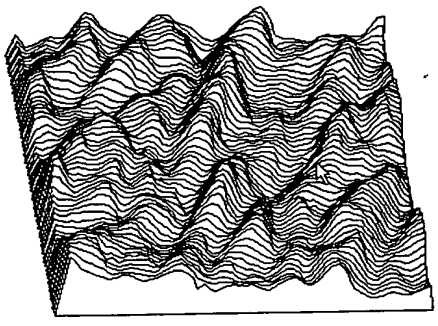

Fig. 7

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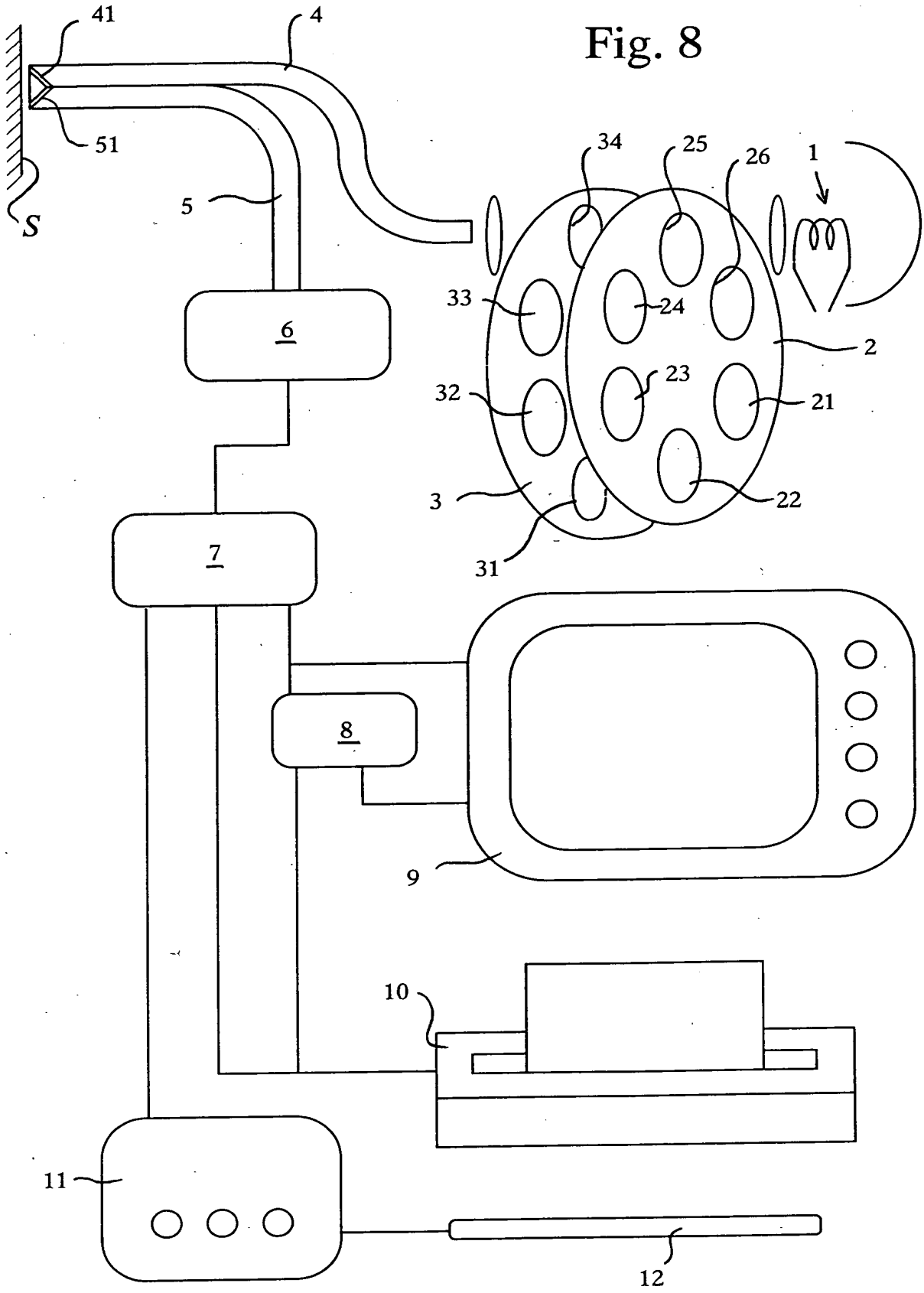
Fig. 8



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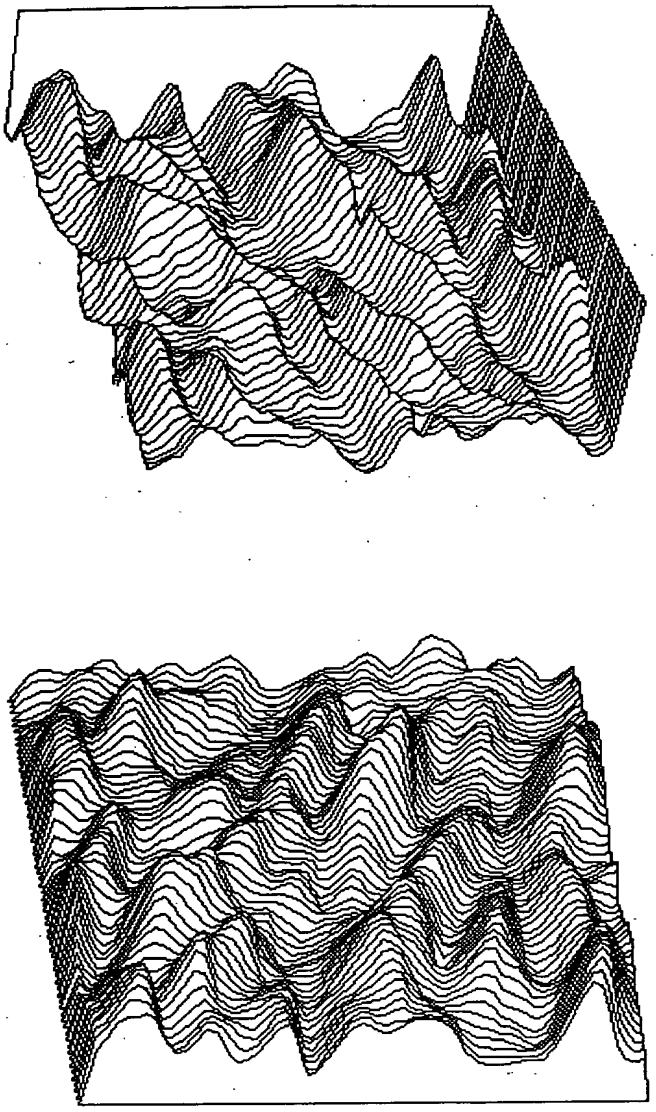

Fig. 9

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